THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.848/MAS/2002, dated 15/11/2002 by Orchid Chemicals & Pharmaceuticals Ltd., having its registered office at 1, 6th Floor, Crown Court, 34, Cathedral Road, Chennai 600 086, Tamil Nadu, India.

.....In witness thereof

I have hereunto set my hand

Dated this the 9th day of December 2003
18th day of Agrahayana, 1925(Saka)

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet,Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Orchid Chemicals & Pharmaceuticals Ltd., an Indian company having its registered office at 1,6th Floor, Crown Court, 34, Cathedral Road, Chennai - 600 086, TN, India hereby declare

1.(a) that we are in possession of an invention titled **AN IMPROVED PROCESS FOR THE PREPARATION OF CEFDINIR**

(b) that the complete specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

1. Pandurang Balwant Deshpande
F-3, Sand Stone Apartment,
First Avenue, Indira Nagar,
Chennai 600 020, Tamilnadu, INDIA

2. Chandrasekaran Ramasubbu
No. 3 (New No.7)
B1, Rammiyam Foundation, 7th Main Road,
Dhandeeswarnagar, Velachery,
Chennai-600 042, Tamilnadu, INDIA

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Dr. C. B. Rao
Orchid Chemicals & Pharmaceuticals Ltd.,
1,6th Floor, Crown Court,
34, Cathedral Road, Chennai - 600 086, TN, India

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
Pandurang Balwant Deshpande

(Signed) _____
Chandrasekaran Ramasubbu

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application

(a) complete specification (15 pages, in triplicate)

(b) abstract of the invention (1 page, in triplicate)

(c) fee Rs. 5000.00 (five thousand rupees only) in cheque bearing 219168 dated November 06, 2002, drawn on ICICI bank, Chennai.

We request that a patent may be granted to us for the said invention

Dated this fourteenth (14th) day of November 2002

(Signed) _____
Dr. C. B. Rao
Dy. Managing Director
Orchid Chemicals & Pharmaceuticals Ltd

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

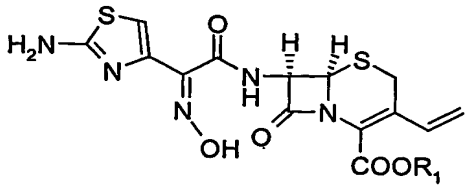
AN IMPROVED PROCESS FOR THE PREPARATION OF CEFDINIR

Orchid Chemicals & Pharmaceuticals Ltd.
an Indian Company having its registered office at
1,6th Floor, Crown Court,
34, Cathedral Road
Chennai - 600 086, TN, India

The following specification describes the nature of the invention and the manner in which it has to be performed :

Field of the Invention

The present invention relates to an improved process for the preparation of cephalosporin antibiotic. More particularly, the present invention relates to a process for the preparation of cefdinir of the formula (I).



(I)

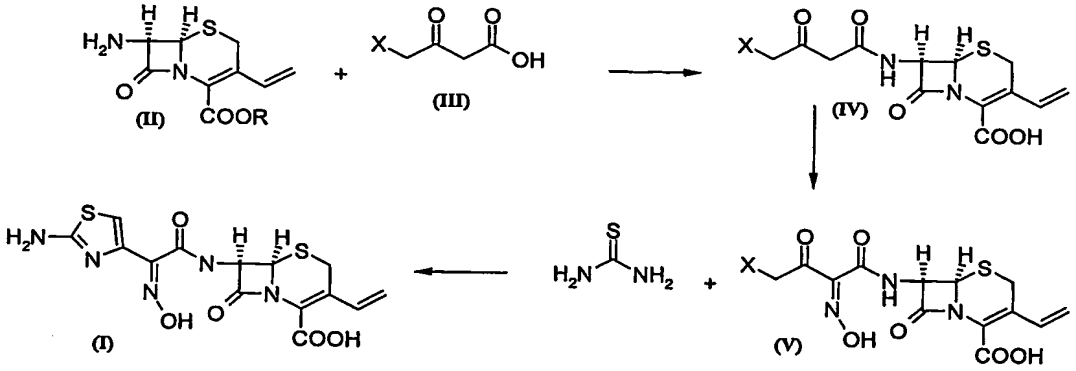
wherein R_1 represents hydrogen, carboxylic acid ester or easily cleavable carboxylic protecting group.

The present invention also provides new salts of compound of formula (VIII) and a process for the preparation of cefdinir using the new salts.

Background of the Invention

Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum over the general gram positive and gram negative bacteria, especially against *Streptococci,* than other antibiotics for oral administration.

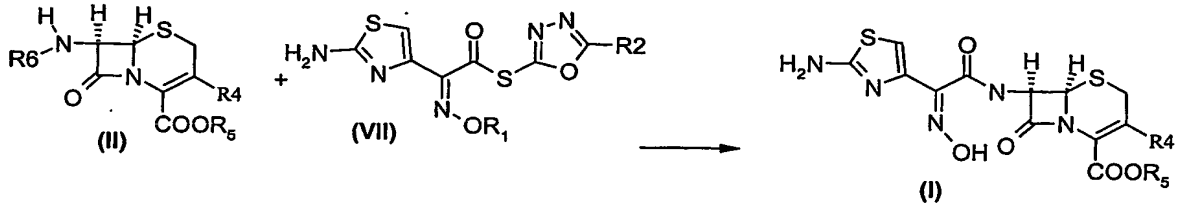
In view of the vital antibiotic activities of cefdinir of the formula (I), various methods of preparation were reported. US patent No. 4,559,334 discloses a process for the preparation of cefdinir as depicted in the Scheme I.



Scheme I

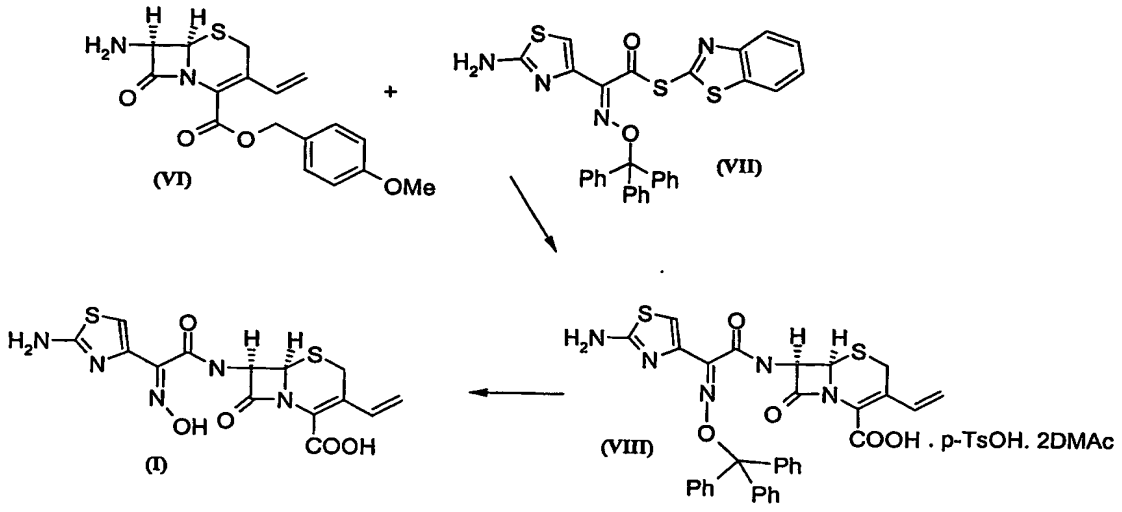
In the disclosed process, 7-amino-3-vinyl-3-cephem-4-carboxylic acid ester is acylated with the reactive ester of haloacylacetic acid, which was converted to its oxime, followed by cyclization with thiourea and deprotection of the ester group to afford cefdinir. The cyclization step suffers from poor yield and affords brownish color of the thiazole derivative, which subsequently affords cefdinir, but quality and yield were inferior. Further, owing to the fact that the expensive 7-amino-3-vinyl-3-cephem-4-carboxylic acid is carried through four steps, cost of producing cefdinir is high.

In our US patent No. 6,388,070 disclosed a process for preparing a compound of formula (I), wherein, R_1 represents H, trityl, etc., R_2 represents H, phenyl, etc., R_3 represents H or C_1 -C_7 alkyl; R_4 is CH_3, CH=CH, etc., R_5 is H or a salt or a carboxylic protecting group; R_6 is H or trimethylsilyl; comprising acylating the compound of formula (II) with compound of formula (VII) in the presence of an organic solvent, organic base and a silylating agent at a temperature in the range of -10 °C to +30 °C. The reaction is shown in scheme II below :



Scheme II

US patent No. 6,093,814 discloses a process for the preparation of cefdinir and its intermediate as represented in the Scheme III:



Scheme III

In this process 7-amino-3-vinyl-3-cephem-4-carboxylic acid is condensed with 2-benzothiazolyl (z)-(2-aminothiazol-4-yl)-2-(z)-(trityloxyimino)acetate in N,N-dimethyl acetamide, and the product obtained was treated with p-toluenesulfonic acid in the presence of a mixture of diethyl ether and methanol to get crystalline 7-[(2-aminothiazol-4-yl)-2-(z)-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid.pTSA.2DMAc solvate. This process utilizes highly volatile, low-boiling and therefore industrially-not-preferred solvent, diethyl ether, for crystallizing out the above solvate. In addition, the quantity of the low-boiling solvent used is also very high ranging from 60-100 volumes, thereby adding hazard to the operations. Added to this is the fact that the recovery of these solvents from their mixture is not straight-forward.

US patent No. 6,350,869 discloses the purification of impure cefdinir through the preparation of N,N-dicyclohexylamine salt of 7-[2-aminothiazol-4-yl-2-(z)-hydroxyimino acetamido]-3-vinyl-3-cephem-4-carboxylic acid and subsequent hydrolysis to get pure cefdinir. This process requires the preparation of crude

cefdinir, conversion to N,N-dicyclohexylamine salt and then hydrolysis of the salt to get pure cefdinir, and therefore the overall yield is not attractive.

US patent No. 6,350,869 also emphasizes that cefdinir is unstable in the presence of other amines, with which, it gets heavily degraded. In addition, Yoshihiko Okamoto et al. (J. Pharm. Sci. Vol. 8S(9), 976, 1996) report that cefdinir may be unstable under basic environment.

Considering the foregoing limitations, we undertook an investigation in our lab to identify a process, which involves (i) less number of steps, (ii) the direct isolation of cefdinir, with out the need to prepare crude cefdinir in an additional step and (iii) a simple method of crystallizing out the solvate of the formula (II), without employing low-boiling solvents/mixture of solvents. This would permit commercializing the production of high-pure cefdinir with industrial-friendly solvent, which can further be recovered for recycling.

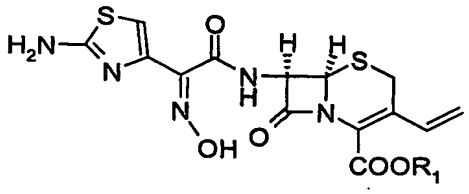
Objectives of the Invention

The main objective of the present invention is to provide a commercially viable process for the preparation of cefdinir of the formula (I), which would be easy to implement on manufacturing scale.

Another objective of the present invention is to provide new salts of formula (VIII), which are insoluble and stable throughout the process of producing the cefdinir cephalosporin and a process for the preparation of cefdinir using these new salts.

Summary of the Invention

Accordingly, the present invention provides an improved process for the preparation of cefdinir of the formula (I)



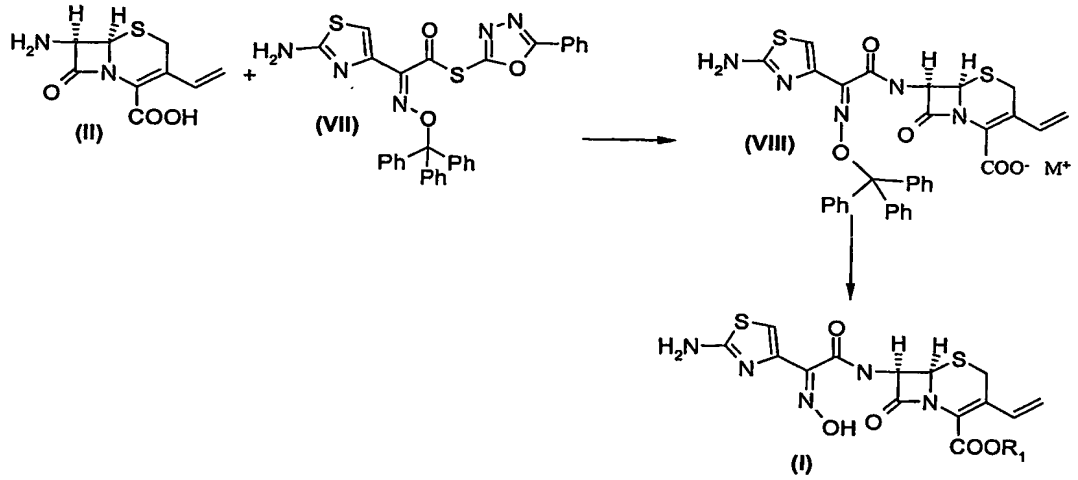
(I)

wherein R_1 represents hydrogen, carboxylic acid ester or easily cleavable carboxylic protecting group, the said process comprising the steps of :

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (II) wherein R_1 is as defined above with compound of the formula (VII) in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (VIII), wherein M^+ is a counter ion,

ii) hydrolyzing the compound of the formula (VIII) using an acid in the presence of a solvent to produce cefdinir of formula (I).

The reaction is shown in scheme-IV below :



Scheme IV

Detailed description of the invention

In an embodiment of the present invention, the counter ion represented by M is selected from sodium, potassium, lithium, magnesium, ammonium,

dicyclohexylamine, N,N'-dibenzylethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine and the like.

In an another embodiment of the present invention, the tertiary amine used in step (i) is selected from triethylamine, N-methylpiperidine, N,N-diisopropylethylamine, trimethylamine and the like.

In yet another embodiment of the present invention, the organic solvent used in step (i) is selected from ethanol, methanol, isopropanol, THF, cyclohexanol, acetone, butan-2-one, acetonitrile, DMAc, water or a mixture thereof.

In yet another embodiment of the present invention, the base used in step (i) is selected from sodium hydroxide, sodium acetate, sodium 2-ethyl hexanoate, potassium hydroxide, ammonium hydroxide, calcium hydroxide, dicyclohexyl amine, N,N'-dibenzylethylenediamine diacetate, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine, and the like.

In another embodiment of the present invention, the acid employed in step (ii) is selected from HCl, sulfuric acid, formic acid, acetic acid, aromatic/aliphatic sulfonic acids such as benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, methanesulfonic acid, triflic acid, and the like.

In yet another embodiment of the present invention, the organic solvent used in step (ii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water and the like or mixtures thereof.

In yet another embodiment of the present invention, the compound of formula (I) obtained is a syn isomer.

In another embodiment of the present invention, easily cleavable carboxylic protecting group is selected from methoxybenzyl, p-nitrobenzyl, diphenylmethyl, t-butyl and the like.

The foregoing technique has been found to be markedly attractive, both from commercial point of view, as well as from manufacturing viewpoint, and affords good quality of cefdinir of the formula (I).

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure.

The present invention is illustrated with the following examples, which should not be construed as limiting to the scope of the invention.

Example 1

Step (i)

Preparation of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino) acetate

To an ice-cold suspension of (Z)-(2-aminothioazol-4-yl)-2-(trityloxyimino)acetic acid (25 gm) in tetrahydrofuran (200 ml), triethylamine (10 gm) was added dropwise over 10 minutes at 0-5 °C. Bis-(2-oxo-oxazolidinyl)phosphinic chloride (15.4 gm) was added and stirred for one hour at 0-5 °C. To the reaction mixture 2-mercapto-5-phenyl-1,3,4-oxadiazole (9.8 gm) and triethylamine (5.0 gm) was added dropwise over 15 minutes and stirred at 0-5 °C for 6 – 7 hours. After completion of reaction, chilled water (500 ml) was added at 10-20 °C in 30 – 40 minutes and stirred at 20 °C for 2 hours. Then the slurry was cooled to 5-10 °C and stirred at this temperature for 45 minutes. The product thus obtained was filtered washed with

water (100 ml) and dried at 30-35 °C for 4-5 hours to yield the title compound (50 gm, water content is 40%).

Step (ii)

Preparation of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (25 gm) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetate (155 gm, water content is 40 %) in N,N-dimethylacetamide (150 ml), triethylamine (23 gm) was added drop-wise at 10±2 °C over 30-45 minutes and the resulting mixture was stirred at 20±2 °C for 6-8 hours. The reaction was monitored by HPLC. After completion of the reaction, tetrahydrofuran (125 ml), 10% sodium chloride solution (250 ml) and ethyl acetate (250 ml) were added at 25 °C and stirred for 20 min. The aqueous layer was separated and washed with ethyl acetate (250 ml). To the aqueous layer, ethyl acetate (500 ml) was added, cooled to 10 - 15 °C, and the pH was adjusted to 2.8-3.0 by 1:1 HCl in 30 min. The layers were separated and to the ethylacetate layer, 12 % (w/v) methanolic potassium hydroxide solution (60 ml) was added dropwise in 30 min at 25 °C, and stirred for 45 min. The resulting slurry was filtered, washed with ethyl acetate (150 ml) followed by acetone (150 ml) and dried at 30-35 °C under vacuum to obtain the title compound (45 gm, HPLC Purity >99.0%).

Step (iii)

Preparation of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid

A mixture of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (25 gm) and activated

carbon (2.5 gm) was added to an aqueous acetone solution (1:1, 70 ml) containing p-toluenesulphonic acid (17.7 gm) at 50 °C. The reaction mixture was heated to 70 °C in 20 minutes and maintained at this temperature for 35 minutes. After completion of the reaction, chilled ethylacetate (200 ml) having temperature –15 °C was added to the reaction mixture to reduce the temperature to 30-35 °C. The carbon was filtered and the carbon bed was washed with water (50 ml). The filtrate was diluted with water (200 ml), warmed to 35 °C and pH of the solution was adjusted to 6.0 –6.5 using aqueous ammonia solution (20%). The aqueous layer was separated and treated with carbon (2.0gm) at 35°C for 35 min. The carbon was filtered and the carbon bed was washed with water (50 ml). Acetone (25 ml) was added to the filtrate and 10 % (w/v) solution of sulphuric acid was added dropwise to bring down the pH from 4.5 to 2.8 at 33-35 °C, stirred for 30 minutes and adjusted the pH again to 2.6. The resulting slurry was stirred for 15 – 20 minutes at 33-35 °C, cooled to 20-25°C, and stirred for 30 minutes. The crystals thus obtained was filtered, washed with water (50 ml) and dried at 35 °C under vacuum for 3-4 hours to get the title compound (9.0 gm, HPLC purity < 99%).

Example 2

Step (i)

Preparation of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino) acetate

To an ice-cold suspension of (Z)-(2-aminothioazol-4-yl)-2-(trityloxyimino)acetic acid (25 gm) in tetrahydrofuran (200 ml), triethylamine (10 gm) was added dropwise over 10 minutes at 0-5 °C. Bis-(2-oxo-oxazolidinyl)phosphinic chloride (15.4 gm) was added and stirred for one hour at 0-5 °C. To the reaction mixture 2-mercapto-5-phenyl-1,3,4-oxadiazole (9.8 gm) and triethylamine (5.0 gm) was added dropwise over 15 minutes and stirred at 0-5 °C for 6 – 7 hours. After completion of

reaction, chilled water (500 ml) was added at 10-20 °C in 30 – 40 minutes and stirred at 20 °C for 2 hours. Then the slurry was cooled to 5-10 °C and stirred at this temperature for 45 minutes. The product thus obtained was filtered washed with water (100 ml) and dried at 30-35 °C for 4-5 hours to yield the title compound (50 gm, water content is 40%).

Step (ii)

Preparation of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (5 gm) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetate (24.2 gm) in tetrahydrofuran (40 ml) and water (5 ml), triethylamine (4.6 gm) was added drop-wise at 20±2 °C over 10-15 minutes and the resulting mixture was stirred at 30±2 °C for 6-8 hours. The progress of the reaction was monitored by HPLC. After completion of reaction, ethylacetate (100 ml) and water (75 ml) were added at 30±2 °C and stirred for 20 min. The aqueous layer was separated and washed with ethyl acetate (75 ml). To the aqueous layer, ethylacetate (150 ml) was added, cooled to 10 - 15 °C, and the pH was adjusted to 2.8-3.0 by 1:1 HCl solution in 25-30 min. To the separated ethylacetate layer, acetone (50 ml) and a methanolic potassium hydroxide solution (7.5 % w/v, 20 ml) were added dropwise in 25-30 min at 25 –27 °C and stirred for further 45 min. The resulting slurry was filtered, washed with acetone (2 X 25 ml) and dried at 30-35 °C under vacuum to obtain the title compound (5.0 gm, HPLC Purity >99.0 %).

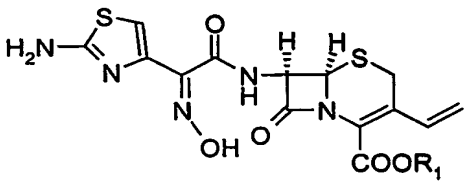
Step (iii)

Preparation of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid

A mixture of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (25 gm) and activated carbon (2.5 gm) was added to an aqueous acetone solution (1:1, 70 ml) containing p-toluenesulphonic acid (17.7 gm) at 50 °C. The reaction mixture was heated to 70 °C in 20 minutes and maintained at this temperature for 35 minutes. After completion of the reaction, chilled ethylacetate (200 ml) having temperature –15 °C was added to the reaction mixture to reduce the temperature to 30-35 °C. The carbon was filtered and the carbon bed was washed with water (50 ml). The filtrate was diluted with water (200 ml), warmed to 35 °C and pH of the solution was adjusted to 6.0 –6.5 using aqueous ammonia solution (20%). The aqueous layer was separated and treated with carbon (2.0gm) at 35°C for 35 min. The carbon was filtered and the carbon bed was washed with water (50 ml). Acetone (25 ml) was added to the filtrate and 10 % (w/v) solution of sulphuric acid was added dropwise to bring down the pH from 4.5 to 2.8 at 33-35 °C, stirred for 30 minutes and adjusted the pH again to 2.6. The resulting slurry was stirred for 15 – 20 minutes at 33-35 °C, cooled to 20-25°C, and stirred for 30 minutes. The crystals thus obtained was filtered, washed with water (50 ml) and dried at 35 °C under vacuum for 3-4 hours to get the title compound (9.0 gm, HPLC purity < 99%).

We claim :

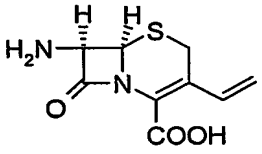
1. A process for the preparation of cefdinir of the formula (I)



(I)

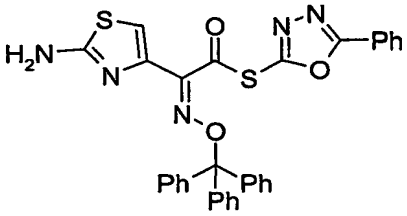
wherein R_1 represents hydrogen, carboxylic acid ester or easily cleavable carboxylic protecting group, the said process comprising the steps of :

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (II)



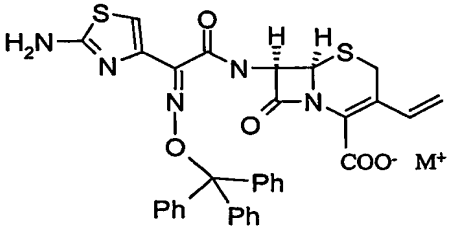
(II)

wherein R_1 is as defined above with compound of the formula (VII)



(VII)

in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (VIII),



(VIII)

wherein M^+ is a counter ion and

ii) hydrolyzing the compound of the formula (VIII) using an acid in the presence of a solvent to produce cefdinir of formula (I).

2. The process as claimed in claim 1, wherein the counter represented by M is selected from sodium, potassium, lithium, magnesium, ammonium, dicyclohexylamine, N,N'-dibenzylethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine and the like.

3. The process as claimed in claim 1, wherein the tertiary amine used in step (i) is selected from triethylamine, N-methylpiperidine, N,N-diisopropylethylamine or trimethylamine.

4. The process as claimed in claim 1, wherein the organic solvent used in step (i) is selected from ethanol, methanol, isopropanol, THF, cyclohexanol, acetone, butan-2-one, acetonitrile, DMAc, water or a mixture thereof.

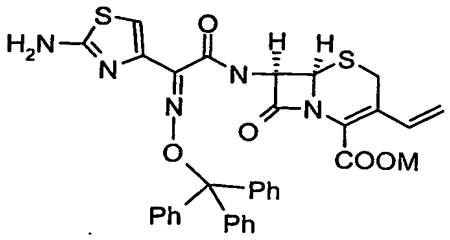
5. The process as claimed in claim 1, wherein the base used in step (i) is selected from sodium hydroxide, sodium acetate, sodium 2-ethyl hexanoate, potassium hydroxide, ammonium hydroxide, calcium hydroxide, dicyclohexyl amine, N,N'-dibenzylethylenediamine diacetate, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine, and the like.

6. The process as claimed in claim 1, wherein the acid employed in step (ii) is selected from HCl, sulfuric acid, formic acid, acetic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, methanesulfonic acid or triflic acid.

7. The process as claimed in claim 1, wherein the organic solvent used in step (ii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water or mixtures thereof.

8. The process as claimed in claim 1, wherein the compound of formula (I) obtained is a syn isomer.

9. A compound of compound formula (VIII),



(VIII)

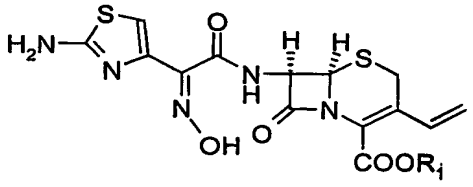
wherein M^+ represents a counter ion.

Dated this fourteenth (14th) day of November 2002
for Orchid Chemicals & Pharmaceuticals Ltd.,

Dr. C. B. Rao
Dy. Managing Director

Abstract

The present invention relates to an improved process for the preparation of cephalosporin antibiotic. More particularly, the present invention relates to a process for the preparation of cefdinir of the formula (I).



(I)

wherein R_1 represents hydrogen, carboxylic acid ester or easily cleavable carboxylic protecting group.